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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,595	10/23/2001	Lino Tavares	208.1005US	8560

23280 7590 06/15/2004

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,595	TAVARES ET AL.	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 20-45* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 20-38, 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' amendment, filed 03/15/2003.

Claims 1-16, 20-38 and 40-45 are included in the prosecution.

Response to Election/Restrictions

1. This application contains claim 39 drawn to an invention nonelected with traverse in the reply filed on 08/25/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. Claims 35 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 35, the expression "rubber-like polymer" does not set out the metes and bounds of the claim. Recourse to the specification does not define the expression "rubber-like polymer". Clarification is requested.

Claim 44 recites the limitation "softening ester" in claim 23. There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive.

Regarding the rejection of claim 35, applicants traverse the rejection by arguing that the "rubber-like synthetic polymers" are known by those skilled in the art, and disclosed by US '711.

In response to the above argument, the examiner agrees that the "rubber-like synthetic polymers" are known in the art, but the "rubber-like synthetic polymers" is broad class that encompasses wide varieties of polymers, copolymers and block polymers, and applicants did not disclose in the specification what specific "rubber-like synthetic polymers" are suitable for their invention.

Regarding claim 44, the claim still lack antecede basis for "softening agent" in claim 23, from which it depends.

Claim Rejections - 35 USC § 103

3. Claims 1-16, 20-38 and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/10781 ('781) in view of US 5,091,186 (186).

WO '871 teaches method for treating hypertension and angina using felodipine (abstract). The reference disclosed that any suitable route of administration may be employed as for example transdermal patches (page 19, lines 28-34). The reference

disclosed a pharmaceutical composition comprising felodipine in an acceptable carrier and other therapeutic ingredients (page 20, lines 1-6).

The reference does not teach the specific delivery profile claimed by the applicants as claimed in claims 1-16. The reference does not teach the structure of the transdermal delivery system as claimed in claims 20-38 and 40-45.

US '186 teaches a transdermal drug delivery device to deliver drugs at therapeutically effective rates for about 20-28 hours (abstract; col.6, lines 4-20; col.7, lines 29-40). The reference teaches the calcium channel blockers as one of the drugs to be delivered by the transdermal delivery device (col.5, line 10). The transdermal device comprises a flexible backing layer, an adhesive drug reservoir layer, and a release liner (col.3, lines 25-30, 6-63; col.4, line 43). The delivery profile of the drug is determined by the diffusivity of the drug in the reservoir layer, the solubility of the drug in the reservoir layer, and the degree of drug loading (col.6, lines 24-44). A given drug loading value will provide certain duration of delivery rate (col.7, lines 18022). To achieve the known desirable blood level of the drug, the delivery rate of the drug ranges from 10-50 ug/cm^2/hr (col.7, lines 47-51). The reservoir is pressure sensitive adhesive comprising rubbers, polysiloxane and polyurethanes (col.4, lines 33-40). The reservoir further comprises solvent and glycol, claimed by applicant as softening agent (col.6, line 1; col.7, line 55).

The claimed amounts of different ingredients in the reservoir layer do not impart patentability to the claims because it is within the skill in the art to select optimal parameters in order to achieve a beneficial effect. Thus, the claimed amounts of the

drug, solvent and the softening agent are not considered critical, absent evidence to the contrary.

The selection of particular solvent and softening agent for a specific drug is within the skill of the art depending on the properties of the each drug and its intended use. Thus the solvents and softening agents claimed in claims 37, 38, 44, and 45, do not impart patentability to the presented claims, absent evident to the contrary.

The determination of the relative release rate via an in-vitro permeation test utilizing a Valia-Chien cell is known in the art and it is not part of the claimed method of treating hypertension and angina; or even a part of the transdermal device that provide particular plasma levels. It is only an in-vitro diagnostic test that is expected to provide the same results obtained from two similar delivery devices tested under the same circumstances, and the recitation of this in-vitro test does not impart patentability to claims directed to method of treating hypertension and angina or claims directed to transdermal device applied to patients to provide plasma levels, i.e. in vivo use.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat hypertension and angina using a transdermal device comprising felodipine, as disclosed by WO '781, and provide the felodipine in the transdermal device disclosed by US '186 that provide a particular delivery profile of the drug, and manipulate the amount of the drug to obtain a specific delivery profile, motivated by the teaching of US '186 that a given drug loading value will provide a certain duration of delivery rate depending on the drug loading, with reasonable

expectation of having a transdermal drug delivery device to deliver felodipine to treat hypertension and angina effectively.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above obviousness rejection by arguing that WO '781 does not teach the delivery profile as claimed in claims 1 and 8. The secondary reference teaches the patch applied for 24 hour then replaced, thus, modification of the reference would have achieved therapeutic blood level for 24 hour only and not for 3-5 days. The reference does not disclose steady state plasma level of felodipine.

In response to the above argument, the examiner position is one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary reference teaches method for treating hypertension and angina using felodipine, and the secondary reference teaches a delivery profile that can be determined by the diffusivity of the drug in the reservoir layer, the solubility of the drug in the reservoir layer, the degree of drug loading that will provide certain duration of delivery rate. The reference further teaches that to achieve the known desirable blood level of the drug, the delivery rate of the drug ranges from 10-50 ug/cm^2/hr, as claimed by applicants. It is expected to obtain the same plasma level from the transdermal patch that deliver

felodipine to the skin at the same rate. Determination of the drug delivery profile and period of administration as well as the dose are within the skill of the art and it is controlled by many variables such as patient's age, weight, severity of the treated condition, etc. The art recognized prolonged application of the patch for more than 24 hour, even by replacing the patch in order to maintain the steady plasma level. In response to applicant's argument that modification of the reference would have not achieved therapeutic the claimed invention, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skill in the art would have been motivated by the teachings of US '186 that a given drug loading value will provide a certain duration of delivery rate depending on the drug loading, with reasonable expectation of modify the drug loading in the device to achieve the desired duration of drug delivery rate according to specific patient condition.

In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or

impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

4. Claims 37, 38, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO '781 in view of US '186 as applied to claims 1-16, 20-38 and 40-45 above, and further in view of US 5,240,711 ('711).

The teachings of WO '781 and US '186 are discussed above.

The combination of WO '781 and US '186 does not teach the specific solvents and specific softening agents as claimed in claims 37, 38, 44, and 45.

US '711 teaches a transdermal drug delivery device for controlled delivery of drug comprising backing layer, polymeric reservoir and protective liner. The reservoir comprising: 20-90% of polymeric material, 0.1-20% of the drug, 0.1-30% softener, and 0.1-30% of solvent (abstract; col.1, line 64-67; col.4, line 23). The reservoir is pressure sensitive adhesive and contains rubber-like co-, homo-, or block-copolymers (col.3, lines 25-26). The solvents used include those contain at least one acidic group, monoesters of dicarboxylic acids, such as monoethyl glutarate (col.4, lines 13-16). The softeners include medium chain triglycerides of the caprylic/capric acids or coconut oil; and dodecanol (col.3, lines 63-68; col.4, lines 1-2; col.7, lines 25-29). The backing is flexible, inflexible or aluminum foil (col.7, lines 5-12).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat hypertension and angina using a transdermal device comprising felodipine that provides a specific delivery profile and having particular

structure, and select the specific solvents and softening agents disclosed by US '711, motivated by the teaching of US '711 that the transdermal device having these particular ingredients in its reservoir layer provides a controlled delivery of the drug, with reasonable expectation of having a transdermal drug delivery device to deliver felodipine to treat hypertension and angina effectively.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above rejection by arguing that US '711 only teaches buprenophine transdermally, thus, one skilled in the art would not combine US '711 with WO '781 in order to produce felodipine transdermal delivery system the deliver the claimed profile, and even if combined would not arrive at the claimed invention.

In response to the above argument, the examiner position is US '711 is relied upon for the solely teaching of the solvents and softening agents that are known in the art and widely used in conventional transdermal devises for controlled release of drugs. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 5,045,319 disclosed transdermal delivery system to deliver cardiovascular pharmaceuticals wherein the in-vitro release studies can be conducted using Valia-Chien diffusion cell.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis Ghali
Examiner
Art Unit 1615

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